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Case Report

Immune Thrombocytopenia Following Dengue Fever

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Abstract

Introduction: Dengue is an endemic mosquito-borne infection in tropical countries. The manifestations vary from asymptomatic infection to classic dengue fever, to more critical forms like dengue hemorrhagic fever and dengue shock syndrome. The critical phase occurs typically within the timeline of 4-7 days from the onset of symptoms.

Case Report: We, hereby, report the case of a 7-year-old girl child who initially recovered from classic dengue fever. However, she was readmitted 18 days after the onset of initial symptoms with major bleeding manifestations due to immune thrombocytopenia responding to intravenous immunoglobulin.

Discussion: Dengue fever may be associated with mild to moderate thrombocytopenia in the febrile phase and moderate to severe thrombocytopenia in the critical phase. Here, the index case developed thrombocytopenia much after the expected critical phase was over.

Conclusion: Awareness of this possibility and continued monitoring, even after apparent recovery from dengue, is important for detecting and managing late-onset thrombocytopenia.

Keywords: dengue fever, immune thrombocytopenia, child

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1. Introduction

Dengue infection is a major public health problem in the Indian subcontinent caused by the dengue virus (DENV) having 4 serotypes DEN1, DEN2, DEN3, and DEN4 belonging to the *Flaviviridae* family transmitted by *Aedes aegypti* mosquito. The disease severity can vary from asymptomatic infection to classic dengue fever to more severe forms like dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Dengue timeline is traditionally divided into 3 phases - febrile phase, critical phase, and recovery phase. Varying degrees of thrombocytopenia may be associated with dengue fever, the exact cause of which remains unclear, although various mechanisms have been hypothesized [1, 2].

Immune thrombocytopenia (ITP) is a platelet antibody-mediated peripheral destruction of platelets, which may be primary when the etiology is not known or secondary when associated with a certain infection like TB, HIV, HBV, HCV, collagen diseases like systemic lupus, and certain drugs like quinine and heparin [3, 4]. Secondary ITP following dengue infection has rarely been reported in literature. We hereby report the case of a child suffering from dengue fever in whom symptomatic thrombocytopenia with major bleeding manifestations developed long after the critical phase, and which responded satisfactorily to intravenous immunoglobulin infusion.

2. Case Description

A 7 year old, previously healthy, girl was referred with a history of 3 days of high-grade fever, myalgia, and retro-orbital pain. She also had several episodes of vomiting since that morning. She had received paracetamol for fever but there was no history of intake of any NSAIDs. There was a confirmed history of dengue infection in one of her siblings and 2 members of her neighbor's family in the recent past. At presentation, the child was conscious and oriented but sick looking. Her body temperature was 103°F. Her vitals were normal (heart rate 76/min, respiratory rate 18/min, BP-98/60 mmHg which was 50th percentile for age, sex, height, SpO_2 of 96% in room air). There was no rash, abdominal pain, decreased urine output, pallor, icterus, or organomegaly. Her anthropometric parameters were within the normal limits.

After sending blood and other body fluid samples for culture and other routine tests, she was started on symptomatic and supportive treatment with constant monitoring of blood pressure and other vitals. The test reports at the presentation are summarized in Table **1**.

With a positive dengue NS1 antigen report, she was managed as a case of classic dengue fever. With 6 hourly monitoring of platelet counts and PCV, the former ranging from 60,000-1,10,000/mm^3 and the later remaining normal throughout. The fever subsided on day 3 of admission with a gradual return of a feeling of well being. After observing her clinically and with lab investigations for 2 more days, she was discharged in a stable condition (after 8 days of fever onset).

However, this story did not remain as uneventful as it seemed initially with an undesirable and rare twist. Unexpectedly, she was brought to ER 10 days after discharge with bilateral subconjunctival bleeding,

Table 1: Summary of lab investigation reports at presentation.

Parameter (unit)		Parameter (unit)	
Hemoglobin (g/dl)	10.2	Dengue NS1 (ELISA)	Positive
PCV	36.2	Malarial parasite	Negative
Total leucocyte count (/mm^3)	3100	Malarial antigen	Negative
Differential count		Blood culture	Negative
Platelet count (/mm^3)	60,000	Urine culture	Negative
C-Reactive protein (mg/dl)	1.8	Scrub IgM (Done on day 7 of fever)	Negative
Serum creatinine (mg/dl)	0.6	Leptospira IgM and IgG (on day 7 of fever)	Negative
Serum Na + (mmol/l)	136	Dengue by MAC ELISA IgM (on day 7)	Positive
Serum K + (mmol/L)	5.3	Dengue IgG (on day 7)	Negative
Urine routine	Normal	Chikungunya IgM by MAC ELISA	Negative
Serum albumin(g/dl)	4.3	Chest Xray	Normal
Serum bilirubin(mg/dl)	0.8	USG of abdomen	Normal

passage of red urine, and petechial spots all over her body. She was afebrile, conscious, and oriented. Heart rate, respiratory and blood pressure were within normal limits. She also had excessive bleeding from venipuncture sites. No signs of plasma leakage were observed. Her hemoglobin was reported 9.6g/dl, a total leucocyte count of 8,200/mm^3, and a platelet count of 22,000/mm^3, and urine routine examination reported plenty of RBC. As her platelet count dropped to 5000/mm^3 over the next 24 hr with worsening of bleeding, she was transfused with 4 units of single donor platelet concentrate; however, even after this, her platelet count remained at 6000/m^3.

Other relevant investigations during this admission episode were serum ferritin 53 ng/ml, triglyceride level 128 mg/dL, prothrombin time 11sec (INR1.1). Antinuclear antibody by IF was negative. HIV, HBsAg, HCV IgM, IgM VCA for EB virus, and parvovirus antibody were negative. Sputum for CBNAAT for Mycobacterium tuberculosis was also negative.

As this symptomatic thrombocytopenia appeared more than 15 days after the onset of fever without any sign of plasma leakage, typical of the dengue critical phase, and as thrombocytopenia did not improve even after repeated platelet transfusion, immune-mediated peripheral destruction of platelet was considered as the possible etiology. This was corroborated when the mean platelet volume was reported as 13.9 µm^3(N- 8-11). Bone marrow study was also done which reported normal except the presence of megakaryoblasts.

With a diagnosis of immune thrombocytopenia following a dengue infection, she was given IVIg at 1 gm/kg. Her platelet count improved dramatically to 50,000/mm^3 6 hr after IVIg infusion with a gradual subsidence of bleeding manifestations with platelet count reaching to 1,20,000/mm^3 48 hr after infusion. She was discharged on day 7 of admission on a platelet count of 2,10,000/mm^3. She remained asymptomatic with normal platelet count on follow-up till 6 months of the initial episode.

3. Discussion

This is the story of a 7-year-old girl who initially suffered from uncomplicated classic dengue fever, discharged in a satisfactory condition. But there was an unexpected twist in the tale when she was readmitted with severe bleeding manifestations associated with severe thrombocytopenia much beyond the typical timeline of the critical phase.

Various mechanisms have been hypothesized to explain dengue-associated thrombocytopenia including virus-induced bone marrow hypoplasia, immune or non-immune mediated peripheral destruction of platelets, and even platelet consumption due to ongoing coagulopathy [1, 2]. There are even some reports of inherited syndromal causes of thrombocytopenia presenting at a later age [3]. But that possibility was ruled out here as there were no associated anomalies. As the child was afebrile, active, and not sick-looking with normal hemoglobin and total count, normal CRP, normal ferritin, triglyceride level, the possibility of bone marrow suppression due to HLH was reasonably ruled out. Nonresponse to platelet transfusion and increased mean platelet volume and bone marrow megakaryoblasts favored a diagnosis of immune thrombocytopenia. A remarkable improvement with IVIg corroborated it.

The thrombocytopenia in the initial phase of dengue is hypothesized to be due to the suppression of bone marrow by the virus. Subsequently, in the critical phase, it is mostly due to immune-mediated peripheral platelet destruction which is corroborated by the fact that patients with dengue fever have been shown to have IgM antiplatelet antibodies. But this thrombocytopenia is transient and recovers on its own. Immune-mediated thrombocytopenia giving rise to significant bleeding manifestation much after the critical phase is over, is rare [2].

A wide range of viruses have been implicated in the etiopathogenesis of ITP, especially in children, which include human immunodeficiency virus (HIV), hepatitis C, varicella-zoster, and Epstein-Barr virus (EBV), although the exact roles of these viruses in the pathogenesis of this disorder remains unclear. It is hypothesized that viral antigens mimic platelets stimulating the formation of platelet autoantibodies. Due to resource constraints, specific dengue serotypes and antiplatelet antibodies could not be done in the index case. Some reports indicate an association of ITP with DEN3 [3-5].

Table **2** summaries the previous publications on this association and compares them with our index case [6-11]. Two case reports, one in an adult female and another in a 14-year-old boy from Brazil [6] and Sri Lanka [7], respectively, describe chronic ITP following dengue hemorrhagic fever. Prasanth et al. [8] describes a child succumbing to intracranial and pulmonary hemorrhage due to persistent and refractory thrombocytopenia during the course of dengue hemorrhagic fever. Boo et al. [9] describes a 13-year-old child succumbing to intracranial hemorrhage 6 months after dengue fever refractory to intravenous methylprednisolone. IVIg was given when blood had already occurred in the terminal stage. Our index child developed acute ITP about 15 days after classic uncomplicated dengue fever without ever showing any features of dengue hemorrhagic fever.

Table 2: Summary of comparison of previous cases reports and our index case.

Author	Place/year	Patient profile	Diagnosis	Treatment given
De Souza et al.	2005/Brazil	47 year/female	Chronic ITP following DEN3	Oral prednisolone
Prasanth et al.	2011/Hubli, India	5 year/male	Intracranial and pulmonary hemorrhage with ARDS/VAP, persistent thrombocytopenia	Single donor platelet transfusion, IVIg, and anti D >. Patient succumbed to hypovolemic shock.
Thadchanamoorthy V	2020/Sri Lanka	14 year/male	Chronic ITP following dengue hemorrhagic fever	Good response to oral prednisolone
Boo et al.	2019/Johor/Malaysia	13 year/male	Intracranial bleeding due to persistent ITP following dengue fever	Patient succumbed despite IVIg and methylprednisolone infusion
Ashrudin NAM	2021/Malaysia	4 year/male	Acute ITP following dengue fever	Good response to oral prednisolone
Present case	2024/Bengal, India	7year/female	Acute ITP following dengue fever	Dramatic response to IVIg infusion

4. Conclusion

ITP should be considered as a differential for thrombocytopenia following dengue infection. It poses a diagnostic challenge, especially when it presents with major bleeding after the conventional timeline of the critical phase is over. Larger well well-designed studies may throw more light on this intriguing aspect of dengue which could pave the way to formulate robust guidelines regarding the management of thrombocytopenia associated with dengue fever. Meanwhile, awareness of this possibility, continued monitoring even after apparent recovery and timely management is important to salvage such patients from unexpected morbidity and mortality.

Acknowledgment

None.

Statement of Ethics

Single case report.

Ethical Approval

Permission was granted by the Chairperson ofInstitutional Ethics Committee, North Bengal Medical College, Darjeeling, WB vide letter no. IEC/NBMC/21/10.6.24

Patient Informed Consent Statement

Written patient informed consent was obtained from the parents to publish their case. No images are involved.

Conflict of Interest

None.

Funding / Support Sources

None.

Author Contribution

Both MN and NG were involved in patient diagnosis, patient care, planning of investigations, and management. MN reviewed the literature. Both MN and NG drafted the manuscript. The final manuscript was approved by both. MN will take the primary responsibility for communication with the journal during the manuscript submission, peer-review, and publication process.

Data Availability Statement

Authors undertake to publicly make their research data set available both pre and post-publication.

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